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Increased Risk of Lymphoma in Sicca Syndrome

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The risk of cancer was ascertained in 136 women with sicca syndrome followed at the National Institutes of Health (NIH). Seven patients developed non-Hodgkin's lymphoma from 6 months to 13 years after their first admission to NIH. This was 43.8 times ($P < 0.01$) the incidence expected from the rates of cancer prevailing among women of the same age range in the general population during this time. In addition, three cases of Waldenström's macroglobulinemia occurred in this study group. Eight patients developed cancers other than lymphoma, similar to the number expected based on the rates prevailing in the general population. Patients with a history of parotid enlargement, splenomegaly, and lymphadenopathy had an increased risk of lymphoma. These clinical conditions did not appear to be early manifestations of undiagnosed lymphoma but rather seemed to identify a subgroup of patients with sicca syndrome with marked lymphoid reactivity, who had a particularly high risk of subsequently developing lymphoma.

SICCA SYNDROME, also known as Sjögren's syndrome, is a chronic, inflammatory, autoimmune disease in which the salivary and lacrimal glands are damaged, producing xerostomia and xerophthalmia. The diagnosis is based on the presence of keratoconjunctivitis sicca, xerostomia, and the characteristic lymphoid infiltrate of the minor salivary glands of the lip. Another connective tissue disease may or may not be present (1). Clinical findings associated with sicca syndrome include renal tubular acidosis (2, 3), interstitial pneumonitis (4), and myopathy (5). Antibodies to a specific acidic, extractable nuclear antigen are frequently present (6-8). The cause is unknown but specific genes of the major histocompatability complex are a prerequisite for the development of the disorder (9-11).

In 1963, Bunim and Talal (12) described three cases of malignant lymphoma and one case of Waldenström's macroglobulinemia among 58 patients with sicca syndrome at the National Institutes of Health (NIH). Subsequently, several case reports have supported the suspicion of an association between sicca syndrome and lymphoma (13-16), Waldenström's macroglobulinemia (14, 16, 17) and lymphoid hyperactivity (pseudolymphoma) (14, 16). However, no estimates have been made of the magnitude of the risk of cancer among patients with sicca syndrome. In this study, the case records of patients with sicca syndrome were analyzed to estimate the risk of lymphoma and search for clinical features associated with its development during the course of the disease.

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Materials and Methods

THE FOLLOW-UP STUDY

The study group consisted of all 142 patients with a confirmed discharge diagnosis of sicca syndrome who were first admitted to the NIH Clinical Center between 1 January 1954 and 31 December 1975. The diagnosis of sicca syndrome was considered confirmed when patients had clinical, laboratory, and histologic evidence of keratoconjuctivitis sicca and xerostomia. All patients had typical focal infiltrates of small lymphocytes in the minor salivary glands found on diagnostic lip biopsy. Malignant lymphoma was diagnosed in two patients before their first admission to NIH, and they were omitted from the analyses pertaining to that condition. Three persons with other malignancies diagnosed before their first admission were omitted from the number at risk of developing other malignancies but were included in those at risk of developing malignant lymphoma.

The referring physicians of patients who were no longer being actively followed at NIH as of 30 June 1976 were contacted to ascertain the vital status of each patient, treatments administered, and whether the patient had developed a malignancy. Patients who could not be traced through a referring physician were contacted directly. Reports of deaths were confirmed by obtaining death certificates from state vital records divisions.

Observed cases of cancer in the study group were compared with those that would have been expected based on the experience of the general population (18). Age and time-specific cancer incidence rates from the Connecticut Cancer Registry for the time covered by the study were available (19, 20). Expected numbers of cases in the study group were obtained by applying age, sex, and time-specific incidence rates experienced by the comparison population to the number of person-years of follow-up in the study group. The expected numbers of cases were then summed to obtain the total expected for malignant lymphoma and other cancer. The strength of association is presented as the Relative Risk (RR) estimated by the ratio of observed cases to expected cases. A RR of 2 would indicate, for example, that the number of cases of cancer observed in the study group was twice what would be expected based on the experience of the general population with a similar age distribution. Statistical significance of the difference of this RR from 1.0 (no associa-

tion) was ascertained, assuming an underlying Poisson distribution (21).

Detailed information on age, race, certain clinical aspects of sicca syndrome, and treatments received was obtained for each of the patients from NIH medical records. Several analyses were done on subsets of the total group in an attempt to identify risk factors for the development of lymphoma in patients with sicca syndrome. The clinical features abstracted from records on the total series for these analyses were the presence or absence of rheumatoid arthritis, history of parotid gland swelling, age of onset of sicca syndrome, and age at menopause.

THE CASE-CONTROL STUDY

A case-control analysis was undertaken to ascertain the risk of lymphoma among patients with sicca syndrome with various accompanying clinical conditions. Detailed chart review was done on all of the patients with lymphoma and a matched set of patients with sicca syndrome who did not develop lymphoma. Three to four control subjects were matched to each of the seven patients with lymphoma on the basis of age at first admission, date of first admission, and number of times seen at NIH. Clinical conditions of interest (obtained from the summary for each hospital admission) were evidence of any of the following: rash, vasculitis, lymph node enlargement, pulmonary disease, splenomegaly, muscle disease, parotid swelling, and Raynaud's phenomenon. Routine laboratory variables were recorded from the first laboratory report entered for each admission. All relevant information was abstracted for each admission before diagnosis for the cases. Information was collected for each control subject in the same manner up to the date of diagnosis of lymphoma in the matched case (reference date). The RR of lymphoma for patients with sicca syndrome having a specific clinical condition or abnormal laboratory finding on any admission compared with patients with sicca syndrome without such a finding was estimated for each condition by matched pair analysis, accommodating the varying matching ratios (22).

Results

THE FOLLOW-UP STUDY

The large majority of patients with sicca syndrome are women (23). In this series, only six of the 142 patients were men. No malignancies are known to have developed in these six; therefore, the analyses were limited to the 136 women. These women were followed an aggregate of 1098.7 person-years, for an average of 8.1 years per patient. Ninety-five patients were followed for 5 years or longer. By the closing date for this study (30 June 1976) 67 patients (49.3%) were known to be alive, 55 (40.4%) were known to have died, and 14 (10.3%) were lost to follow-up.

Fifteen cases of cancer (other than skin cancer) occurred during the follow-up period. These included seven cases of non-Hodgkin's lymphoma and eight cases of other types of malignancies. The total number of malignancies that would have been expected based on rates in the general population is 6.74 (Table 1). The eight cancers other than lymphoma and skin cancer were approximately what would be expected based on rates in the general population (Table 1). In contrast, the seven cases of lymphoma are 43.8 times the expected number of 0.16 (Table 1). The risk of lymphoma in the sicca syndrome population is approximately 6.4 cases per 1000 per year. A summary of the findings in these cases is given in Table 2.

The presence or absence of seven diagnostic features of sicca syndrome was sought for every patient. These seven were symptoms of keratoconjunctivitis sicca, symptoms of xerostomia, positive labial salivary gland biopsy, positive parotid scan, abnormal salivary flow, Rose Bengal corneal staining, and abnormal Schirmer's test results. The average number of criteria that were positive for the patients with lymphoma was 4.8. The average for those patients with sicca syndrome not developing lymphoma was also 4.8. Comparison of patients with lymphoma with other patients with sicca syndrome for the frequency with which each diagnostic criteria was positive did not show any marked differences.

Pathologic review of lymph nodes and other involved organs from the seven patients with lymphoma showed four cases of diffuse histiocytic lymphoma, two cases of diffuse mixed lymphocytic and histiocytic type with epithelial cell reaction (Lennert's lymphoma) (24), and one case of poorly differentiated lymphocytic lymphoma. All lymphomas were classified pathologically according to the criteria of Rappaport (25).

The risk of lymphoma did not vary according to age or calendar year of diagnosis of sicca syndrome or by age of menopause of the patients with sicca syndrome (Table 1). The risks for patients with sicca syndrome with rheumatoid arthritis (RR=42.9) and with sicca syndrome only (RR=44.4) were similar. There were 68 patients with a history of parotid swelling some time during the course

Table 1. Observed and Expected Cases of Malignancy among Female Patients with Sicca Syndrome

Patient Group	Total Number of Persons at Risk	Observed Cases	Expected Cases	Relative Risk
All malignancies	131*	15	6.74	2.2†
Nonlymphoma malignancies (except skin)	133*	8	6.58	1.2
Lymphoma	134*	7	0.16	43.8†
Lymphoma development in patients with sicca syndrome with				
Rheumatoid arthritis	58	3	0.07	42.9†
No rheumatoid arthritis	76	4	0.09	44.4†
Onset of sicca syndrome < age 45	63	3	0.05	60.0†
Onset of sicca syndrome > age 45	68	4	0.11	36.4†
Menopause < age 45	37	2	0.05	40.0†
Menopause > age 45	46	4	0.07	47.1†
Parotid swelling	68	6	0.09	66.7†
No swelling	66	1	0.08	12.5
Swelling and radiation	7	3	0.01	300.0†
Swelling, no radiation	61	3	0.08	37.5†
Chemotherapy	20	2	0.02	100.0†
No chemotherapy	114	5	0.14	35.7†

* Five of 136 female patients with sicca syndrome developed malignancies (two, lymphoma; three, nonlymphoma) before admission to National Institutes of Health and were omitted from those at risk of malignancy. The three preadmission cases of nonlymphoma and the two preadmission cases of lymphoma were omitted from those at risk for those conditions.

† Significantly different from 1 at $P = 0.01$.

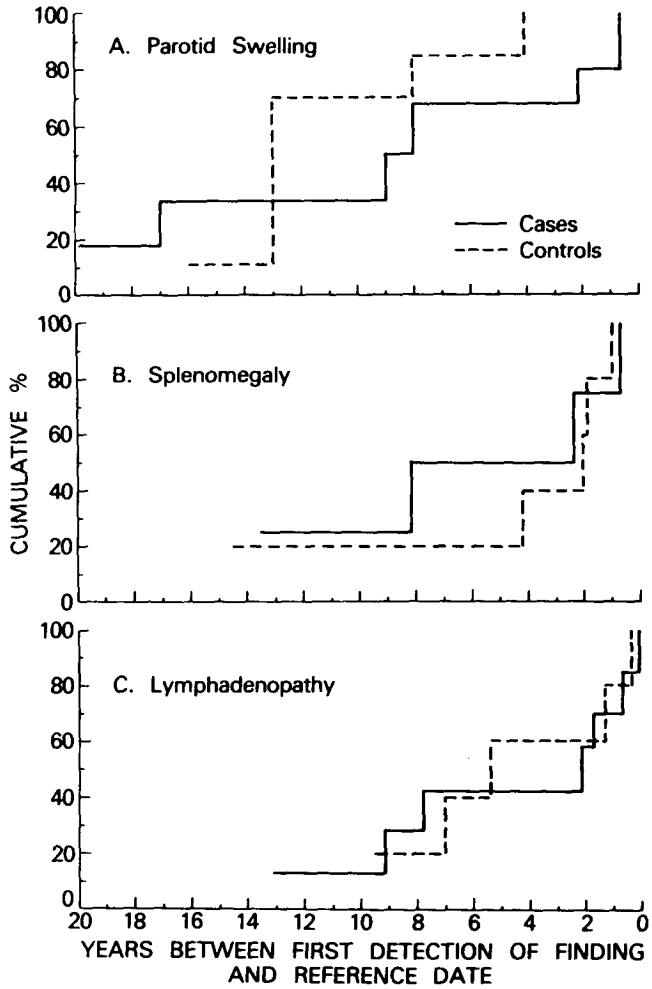

Figure 1. The cumulative occurrence of the three physical findings (parotid swelling, **A**; splenomegaly, **B**; and lymphadenopathy, **C**) that were associated with the eventual development of lymphoma is plotted against the time between the first detection of the finding and the reference date. The reference date for the cases is that of the diagnosis of lymphoma. For the matched control subjects it is the date the corresponding patient developed lymphoma. Only those patients who developed the finding by the reference date are included. The similarity between cases and control subjects indicates that the findings in the case were not manifestations of undiagnosed lymphoma.

of their disease. Among this group, six cases of lymphoma developed compared with 0.09 cases expected (RR = 66.7). Among those 66 patients without a history of parotid swelling, only one case of lymphoma developed (RR = 12.5). There was also a marked difference in the frequency of previous parotid radiation treatment between the patients with lymphoma and other patients with sicca syndrome with parotid swelling who did not develop lymphoma (Table 1). Three of the seven patients with parotid swelling who received local radiation (600 to 2000 rad per gland) developed lymphoma compared with the expected value of 0.01, yielding a RR of 300.0. The period between radiation exposure and diagnosis of lymphoma ranged from 8 months to 15 years. None of the lymphomas arose at the site of irradiation. The RR of lymphoma for patients with parotid swelling who were not irradiated was 37.5 (Table 1).

Twenty patients with sicca syndrome were treated with cytotoxic agents during the course of their disease. One of these developed squamous cell carcinoma of the mouth, and another developed adenocarcinoma of the lung. Two of these patients developed lymphoma (RR = 100.0). The RR of lymphoma in patients who did not receive such agents was 35.7 (Table 1).

Three cases of Waldenström's macroglobulinemia occurred during the follow-up period. All patients with this disorder had monoclonal IgM elevations greater than 3 g/ml. There are no incidence rates available for this disease in the general population, so no expected value could be calculated. However, because this disease occurs much less frequently than non-Hodgkin's lymphoma, the risk must be well over that in the general population. None of the patients who developed Waldenström's macroglobulinemia had received parotid irradiation.

THE CASE-CONTROL STUDY

In this portion of the study the patients with lymphoma were compared with a matched set of patients with sicca syndrome who did not develop lymphoma rather than with the general population as in the previous section. Clinical and laboratory findings at NIH were abstracted from the patient's charts. This portion of the study confirmed the presence of parotid swelling as a risk factor for lymphoma development in patients with sicca syndrome. The RR of lymphoma in the group with parotid swelling documented by physical examination at NIH was 9.2 ($P = 0.01$). Two other risk factors for the development of lymphoma were identified. These were the presence of lymphadenopathy (RR = 3.7, $P = 0.04$) and splenomegaly (RR = 6.7, $P = 0.06$). The cumulative occurrence of these three findings in patients with lymphoma and control subjects who eventually developed them is plotted in Figure 1 against the interval between their first detection and the diagnosis of lymphoma (cases) or the reference date (control subjects). The lack of clustering of these clinical findings in the cases just before the diagnosis of lymphoma indicates that they were not manifestations of undiagnosed lymphoma.

The only significant difference in laboratory variables between patients and control subjects was that the titer of rheumatoid factor was generally higher in the control subjects than in the patients. There were essentially no differences between the patients with lymphoma and the control subjects in tests for hemoglobin, leukocyte count, sedimentation rate, Coombs' test, or positive lupus erythematosus cell preparations. Lack of information on the patients with lymphoma and control subjects from the earlier time periods in this study precluded an adequate evaluation of serum immunoglobulins, antinuclear antibodies, anti-DNA levels, and the presence of cryoglobulins. None of the patients with lymphoma had monoclonal immunoglobulin elevations.

Discussion

The data presented in this paper clearly show that patients with sicca syndrome have a markedly increased risk of a specific type of malignancy, non-Hodgkin's lym-

Table 2. Findings in Patients with Sicca Syndrome with Lymphoma

Patient	Age of Onset of Sicca Syndrome	Age at Diagnosis of Lymphoma	Histologic Type	Parotid Swelling	Radiation Therapy†	Interval Between Radiation and Lymphoma†	Cytotoxic Therapy	Rheumatoid Arthritis	Splenomegaly	Lymphadenopathy
	yrs									
1	59	61	Histiocytic diffuse	+	+	8 months	−	−	−	+
2	57	72	Lennert's*	−	NA	NA	−	+	+	+
3	45	55	Histiocytic diffuse	+	−	NA	+	+	−	+
4	46	67	Lennert's	+	+	NA	+	−	+	+
5	33	50	Histiocytic diffuse	+	+	17 years	−	−	+	+
6	44	55	Histiocytic diffuse	+	+	7 years	−	+	+	+
7	42	42	Poorly differentiated	+	−	NA	−	−	−	+

* Mixed lymphocytic and histocytic, diffuse, with epithelioid cell reaction.
† NA = Not applicable.

phoma. In addition, they appear to have an increased incidence of Waldenström's macroglobulinemia. Although no expected values for macroglobulinemia could be obtained, the risk of its development is probably of comparable magnitude to that of lymphoma. The factors that must be considered as possible causes of the increased risk of lymphoma in sicca syndrome are intrinsic elements of the disease and extrinsic agents to which the patients were exposed, such as ionizing radiation and cytotoxic drugs.

Our data suggest that low-dose parotid irradiation may predispose to lymphoma in sicca syndrome. There is another explanation, however, for this apparent association. The irradiated patients had the most severe salivary gland enlargement, and we have identified this as a factor that increases the risk of lymphoma in the absence of irradiation. Thus the treated patients may have been a subgroup at high risk of lymphoma regardless of X-ray exposure. Although we feel this is a likely explanation for the excess risks associated with irradiation, with these data we cannot rule out a role for the radiation itself. Because of this we would suggest that it not be administered to patients with sicca syndrome.

The small number of patients who received cytotoxic therapy had an increased risk of lymphoma compared with those not so treated. However, this was based on a very few observations and could be due to chance. The excess in the entire patient group was not due to chemotherapy, as there was a 36-fold excess risk of lymphoma for those receiving no chemotherapy. However, because the cytotoxic drugs are immunosuppressive and renal transplant patients and others treated with immunosuppressive drugs also have a high incidence of lymphoma (26, 27), it may be advisable to avoid their use in sicca syndrome.

The risk of lymphoma appears to be increased in a number of other conditions including adult celiac disease (28), malaria (29), and sarcoidosis (30). In addition, there are reports of lymphoproliferation progressing to frank malignancy in patients with rheumatoid arthritis (31), dermatomyositis (32), and systemic lupus erythematosus (33). These are all states of chronic antigenic stimulation in which there is some evidence for loss of immunoregulatory function (34-36). It is possible that in an intensely stimulated immune system undergoing extensive proliferation, a clone of lymphocytes may become autonomous and produce lymphoma.

This hypothesis receives some support from the results of the case-control study. The physical findings associated with an increased risk of lymphoma—parotid swelling, splenomegaly, and lymphadenopathy—are all indicators of extensive lymphoproliferation. They can be used to identify the patients with sicca syndrome who must be followed most closely for the development of lymphoma. Because the risk of lymphoma in sicca syndrome appears related to the severity of the associated lymphoproliferation, the overall risk of lymphoma within any group of patients with sicca syndrome will depend on the frequency and extent of this finding in its members and thus may differ from the experience at NIH.

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